The Quantitative Relation Between T1-Weighted and T2-Weighted MRI of Normal Gray Matter and Iron Concentration

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A retrospective analysis of 158 T1-weighted and T2-weighted MRI scans of normal brains at 0.5 and 1.5 Tesla was performed. Signal intensities in the frontal cortex, caudate nucleus, putamen, and globus pallidus were divided by those of frontal white matter; and these gray/white ratios were correlated with iron concentration, estimated from the anatomical region and age of the patient. Intraregional plots were also made of gray/white ratio versus age for the 1.5 Tesla scans. The changes in both T1-weighted and T2-weighted ratios were consistent with the hypothesis that 1/T1 and 1/T2 vary linearly with iron concentration, and the corresponding coefficients, determined separately from the interregional and intraregional plots, were generally in agreement. Furthermore, the variability of the MRI ratios at 1.5 Tesla was consistent with expected iron variability except for the cortex, in which partial volume errors due to sulci and white matter caused increased variations. The MRI results agreed well with in vitro data on T1 and T2 in tissue specimens and with other MRI studies. When compared with T1 and T2 in ferritin solution, a significant "tissue relaxation enhancement" was found, attributable to slower diffusion and clustering of ferritin in tissue.

Index terms: MRI • Brain • iron • Ferritin • T1-shortening • T2-shortening

Abbreviations: [Fe] = iron concentration, T1W = T1 weighted, T2W = T2 weighted, SIR = signal intensity ratio, RMS = root mean square, SD = standard deviation.

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THE ROLE of brain iron in determining MRI contrast in gray matter is still unresolved. This is true even in the normal brain, let alone in pathologies which may involve more complex chemical changes. In the normal brain, iron is found mostly in the gray matter, particularly (in order of increasing concentration) in the cortex, caudate nucleus, dentate nucleus, putamen, substantia nigra, red nucleus, and globus pallidus (1). The concentrations generally increase with age, with most of the increase occurring in the first 30 years.

A correlation between T2-shortening and brain iron concentration [Fe] has been noted by a number of authors (2–14), both with regard to interregional differences and to age-related changes within a given region. The T2-shortening is generally (but not universally) attributed to diffusion through magnetic inhomogeneities created by ferritin. In fact, two of these studies exploit the dependences of T2-shortening on field strength (13) and on interecho time (14) that are expected from such a mechanism. A similar T2-shortening was noted in the thalassemic spleen and attributed to clusters of hemosiderin, a ferritin-like molecule (15).

Yet, to our knowledge, there has been no demonstration that the correspondence between T2 and iron is total, i.e., that T2 depends only, or almost only, on [Fe] in normal gray matter. In fact, several authors reported finding little or no correlation between T2 (or the related T2*) and [Fe] or age in the normal brain (16–20), and this negative viewpoint was expressed recently forcefully (21). Furthermore, there have been very few mentions of T1-shortening related to iron, despite the presence of such an effect in ferritin solution (22,23). If iron in the form of ferritin is indeed the primary determinant of MRI signal intensity variations in gray matter, the following questions must be addressed: (a) Are both 1/T1 and 1/T2 linearly related to [Fe]? (b) Do both age-related and interregional MRI differences in [Fe] have the same quantitative effect on MRI intensity? (c) Is the intersubject MRI variability consistent with the known variability of [Fe]? (d) Are the MRI changes consistent with NMR relaxation in ferritin solution?

We undertook the present study to try to answer these questions. Mathematically speaking, we tested the

hypothesis that 1/T1 and 1/T2 in normal gray matter have "baseline" values determined by noniron effects, and that they increase from these baselines in proportion to [Fe].

• METHODS

We reviewed MRI studies of normal volunteers, patients with non-neurological disease and epilepsy patients, and selected 158 scans with no radiological evidence of neuropathology. The studies included 26 T1-weighted (T1W) and 31 T2-weighted (T2W) scans at 0.5 Tesla on a Picker Vista scanner, and 53 T1W and 48 T2W scans at 1.5 Tesla on a General Electric Signa scanner. Nominal scan parameters (TR/TE) at 0.5 Tesla were 417/16 msec (T1W) and 2317/100 msec (T2W), whereas at 1.5 Tesla they were 500/12 and 2000/80 msec; slice thicknesses ranged from 3 to 7 mm. A large number of normal child volunteers were included in the 1.5 Tesla group to study iron changes in the early years.

From each study a single slice was selected which best visualized the frontal white matter, prefrontal cortex, caudate nucleus, putamen, and globus pallidus. These regions contain increasing concentrations of iron, ranging from an average of 0.04 mg/g in the white matter to 0.21 mg/g in the globus pallidus (1). Signal intensities were obtained by averaging values from 2 to 5 circular regions of interest, 2.3 mm in diameter, within each unilateral anatomical structure. Gray/white signal intensity ratios (SIRs) were then obtained by dividing the gray matter signal by the white matter signal from the same slice.

In some cases the signal intensities had to be adjusted before taking the ratio, because the scan parameters TR/TE differed slightly from the nominal values above. This was done by using the following equation for MR signal:

$$S = S_o(1 - e^{-(TR-TE)/T1})e^{-TE/T2} \quad (1)$$

where S_o is the (proton density) signal in the limit of zero TE and infinite TR. For the purpose of the correction, nominal values of T1 and T2 from the literature were used. Because both white and gray matter signals were similarly corrected, the resulting changes in gray/white ratio were small, typically < 2%.

Interregional Analysis

For each set of scans, the SIR was plotted versus [Fe], calculated from the equation

$$[Fe] = a_1(1 - \exp^{(-a_2x)}) + a_3 \quad (2)$$

where x is the age of the brain. This equation was obtained empirically by fitting [Fe] data from 98 brains (1). Values of a_1, a_2 and a_3 for each anatomical region are listed in (1).

The plots of SIR versus [Fe] were then fitted with the theoretical equation

$$SIR = A(1 - e^{-(TR-TE)/T1})e^{-TE/T2} \quad (3)$$

where the constant A is equal to S_o divided by the white matter signal intensity. As per hypothesis, 1/T1 and 1/T2 are given by

$$1/T1 = B + C[Fe] \quad (4)$$

and

$$1/T2 = D + E[Fe]. \quad (5)$$

In Equations (3–5), C and E are the parameters of interest that relate relaxation rates to [Fe]; they are the goal of curve-fitting. A is a meaningless scale factor. D, which represents the baseline value of 1/T2, also contributes only to the scale factor and so was set at an arbitrary fixed value. B, the baseline value of 1/T1, interacted so strongly with the other parameters during the fitting (dependency value > 0.99) that a separate determination was not possible; it was therefore fixed at nominal values taken from our ongoing in vitro studies: 1.1 sec^{-1} at 0.5 Tesla and 0.87 sec^{-1} at 1.5 Tesla.

Fitting was done with the MLAB program (Civilized Software, Inc., Bethesda, MD). Because the T1W ratios are affected primarily by C and the T2W ratios primarily by E, an iterative fitting procedure was used. First, C was fitted to the T1W ratios, with E fixed; then, E was fitted to the T2W ratios with C fixed. This process was repeated until there was no significant change in the parameters. Because each parameter was determined by the data set to which it is most sensitive, the convergence was rapid, with only several iterations required. The resulting parameters were well-determined, as indicated by the error estimates and dependency values supplied by the fitting program, and were not influenced by changing the starting values.

Age-Related Analysis

For each anatomical region, T1W and T2W ratios were plotted versus age. This was done only for the 1.5 Tesla studies, which included enough children to make the plots meaningful. These data plots were then curve-fitted with Equations (2–5). For the T1W ratios, only parameters C (and A) were allowed to vary; whereas for the T2W scans, E (and A) were varied. Other parameters were fixed at the values determined earlier.

We want to emphasize that Equation (2) does not predict the iron content of individual brains; only an average, or estimate, for each region and age. This interpopulational comparison is necessary because one obviously cannot measure [Fe] in living humans. Equation (2) comes from the now-classic study by Hallgren and Sourander (1), who extracted non-heme iron from homogenized tissue samples by using 5 N-hydrochloric acid and then measured the iron content colorimetrically by the orthophenathroline method. The iron content was calculated on a fresh weight basis. The parameters for Equation (2) were obtained by empirically fitting the resulting [Fe] versus age scatter plots. No statement of measurement accuracy is given, but the variability of the data, compared with the estimate of Equation (2), ranges from 0.004 mg/g (SE) in the prefrontal cortex to 0.03 mg/g in the globus pallidus, which is about a 10% to 15% variability. Intraregional SD values for subjects over 30 (without curve-fitting) ranged from 15% to 30%. If iron is the causative factor for the MRI changes, we expect to see an MRI variability that is consistent with these deviations of iron concentration [Fe]. We therefore compared the MRI and [Fe] variabilities, taking into account the slope of the curve relating the two, to see if there is consistency.

• RESULTS

Interregional Results

Plots of SIR versus [Fe] are shown in Figures 1–4, along with the theoretical curves. The parameters determined by curve-fitting are given in Table 1. Also shown are the root mean square (RMS) deviations of data

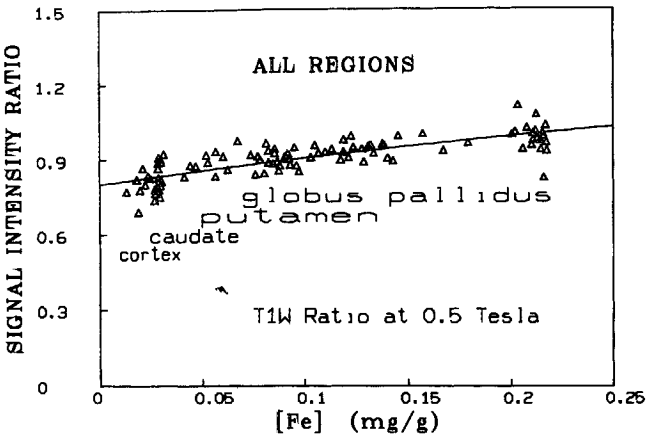


Figure 1. Plot of the T1-weighted SIR at 0.5 Tesla versus estimated iron concentration (1). The data points comprise four "clusters": cortex, caudate, putamen, and globus pallidus, which are spread out and overlap along the horizontal axis because of age-related variations. The solid line is a plot of Equation (3), with parameters C and E determined by curve-fitting.

points about the theoretical curve, divided by the average SIR versus [Fe] slope; this represents the iron (i.e., x-axis) variability that corresponds to the observed SIR (y-axis) deviations.

Age-Related Results

Figures 5 and 6 show intraregional plots of SIR versus age at 1.5 Tesla, along with curve-fits using Equations (2–5). The resulting parameters C and E are listed in Table 2.

Data Variability

Table 3 shows a comparison of SD values for [Fe] (1) and SIR in the four gray matter regions for subjects over 30. For purposes of comparison, the SIR deviations are divided by the average slope of the SIR versus [Fe] curves (Figs 1–4) to give the equivalent [Fe] variability. The SIR variability at 1.5 Tesla is generally comparable to or better than the [Fe] variability, except for the cortex. At 0.5 Tesla, the SIR variability is significantly worse, due to a lower signal-to-noise ratio.

• DISCUSSION

Interregional Plots

Let us return to the four questions asked in the Introduction section. First, it is clear from Figures 1–4 that

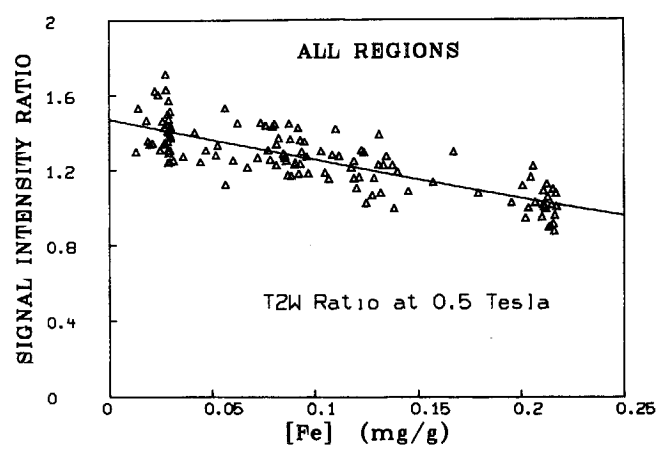


Figure 2. Same as Figure 1, except T2W ratios.

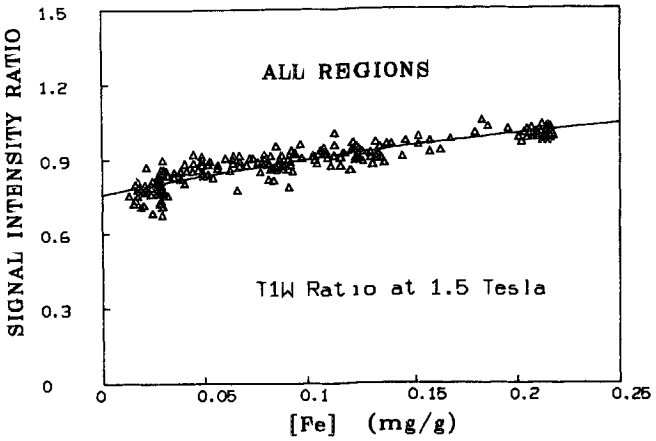


Figure 3. Same as Figure 1, except at 1.5 Tesla.

both T1W and T2W ratios show a consistent trend with increasing [Fe], from the cortex to the globus pallidus, and that this trend is well-fitted by the assumption that 1/T1 and 1/T2 depend linearly on [Fe]. It seems surprising that the correlation of T1 with iron has not been emphasized before.

Intraregional Versus Interregional Comparison

The parameters C and E, determined independently from the intraregional SIR versus age plots (Table 2), are in rough agreement with the interregional values (Table 1) for the globus pallidus and caudate nucleus. (Although the disagreement sometimes exceeds the statistical error estimates in the tables, there are additional error contributions, as noted below, that may account for the differences.) The intraregional/interregional consistency can also be seen visually in Figures 1–4. However the values of C and E in the putamen are about one-half of those in the globus pallidus, and this difference may be outside the margin of error; it could indicate an alteration of the age-related iron effect, or the presence of other age-related factors in this nucleus. On the other hand, another study of 1/T2 versus age (12) produced data which, when Hallgren's formula (1) is applied, show similar coefficients for the putamen and globus pallidus: about 24 sec^{-1} and 28 sec^{-1}/mg Fe/g, respectively. (This study used an interecho time of only 20 msec, which accounts for the lower values, as discussed below.) We believe that more study is needed to fully resolve the question of age-related changes in the putamen.

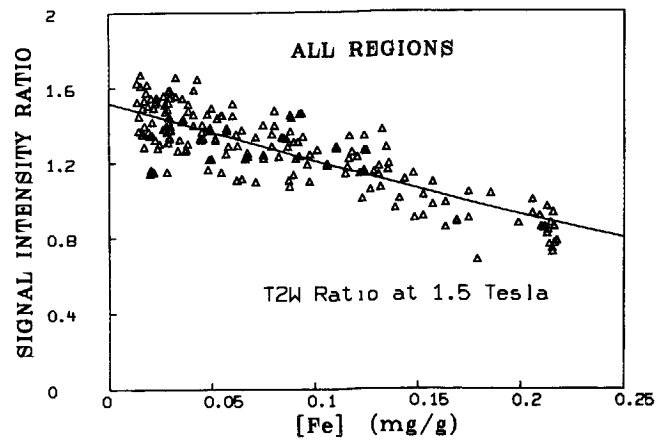


Figure 4. Same as Figure 2, except at 1.5 Tesla.

Table 1
Results of curve-fitting the interregional SIRs (Figs. 1–4)

Ratios	Field (Tesla)	Parameter Value (s^{-1}/mg Fe/g)	RMS Dev	RMS Dev/Slope (mg Fe/g)
T1W	0.5	C = 2.5 (0.2)	0.048	0.050
T2W	0.5	E = 19.8 (1.5)	0.102	0.049
T1W	1.5	C = 2.8 (0.11)	0.039	0.040
T2W	1.5	E = 40.1 (1.6)	0.117	0.035

Note.—Error estimates (in parentheses) are furnished by the fitting program, and are probably underestimates (see text). Also shown are RMS deviations (Dev) of data points from the theoretical curve and the RMS Dev divided by the average slope of the curve.

Variability of Data

The third question concerns the comparison of SIR and iron variabilities. By dividing the SIR variations by the average SIR versus [Fe] slope, we obtain an equivalent iron variability that can be compared with SD values given by Hallgren and Sourander (1). If there are factors other than iron affecting the MRI signal, they would be expected to add to the SIR variability. We see from Table 3 that the SIR SD values at 1.5 Tesla for subjects over 30 are generally consistent with, and sometimes lower than, the [Fe] SD values. The only region which shows significantly increased variability is the prefrontal cortex, and this is clearly due to unavoidable partial volume errors caused by invaginations of sulci and white matter. At 0.5 Tesla, the increased SIR variability is readily attributed to the lower signal-to-noise ratio at this field.

Now let us look at the RMS curve-fitting deviations at 1.5 Tesla (Table 1). They are generally larger than the intraregional SD values of Table 3, because the data covers all ages and all regions, including the cortex with its large partial volume errors, but they still are comparable with the SD values of iron for subjects over 30 (Table 3). They also are comparable with the lower RMS deviations for the [Fe] versus age curves in the globus pallidus and putamen: 0.031 mg/g and 0.026 mg/g, respectively (1). (No value for the caudate was given.) This is not to say that other sources of MRI variability are not present. For example, variations in white matter signal would clearly affect the ratios (13), although this effect is probably very small beyond the age of two (9,20,24). Other possible sources of error are variations in proton density, variations in the baseline values of 1/T1 and 1/T2, and, in older subjects, changes in Virchow-Robin spaces or lacunar infarcts (12). However, the good agreement noted above suggests that these factors are not large.

Comparison with Ferritin

The fourth question is complicated by the obvious differences between tissue and ferritin solutions. For example, slower diffusion times in tissue may increase both spin-spin and inhomogeneity-induced relaxation rates (25). Another difference is that ferritin in tissue is concentrated within cells and organelles, and this "clustering" may increase the T2 relaxation rate due to diffusion, compared with ferritin in solution. The clustering also causes a dependence of 1/T2 on echo time, i.e., an increase for echo times up to about 50 msec (26), which is important when comparing different studies. We refer to these factors, in general, as "tissue relaxation enhancement". Another important difference is that all iron in tissue is not in the form of ferritin.

As for 1/T1, our results for the iron contribution (C in Table 1) are three times greater than the value of about 0.9 sec^{-1}/mg of [Fe]/ml in ferritin solution (loading factor = 1000, T = 37°C) for fields from 0.5 to 1.5 Tesla (22). This difference is consistent with the above concept of tissue relaxation enhancement. The T2 comparison is more complex because ferritin produces two separate contributions to 1/T2: a field-independent (or zero-field) component, and one that increases linearly with field strength (23). It is the latter that is attributed to diffusion through magnetic inhomogeneities created by the ferritin core (see Introduction section). A linear increase of 1/T2 with field strength was also seen in tissue specimens in vitro (26). Unfortunately, our measurements at two field strengths are not sufficient to determine the nature of the field dependence but, assuming it is linear, we can readily convert our values of E at 0.5 and 1.5 Tesla (Table 1) into a zero-field contribution, 9.6 sec^{-1}/mg/g, and a field-dependent contribution, 20.3 sec^{-1}/mg/g/Tesla. When compared with similar results in ferritin solution (loading factor 2650, 37°C) of 0.4 sec^{-1}/mg/g and 3.5 sec^{-1}/mg/g/Tesla (23), we find that the MRI results are 24 times greater for the zero-field component and 6 times greater for the field-dependent component.

Lacking specific knowledge about tissue relaxation enhancement, we cannot go further, other than to note that the differences are at least in the right direction and roughly of the right magnitude.

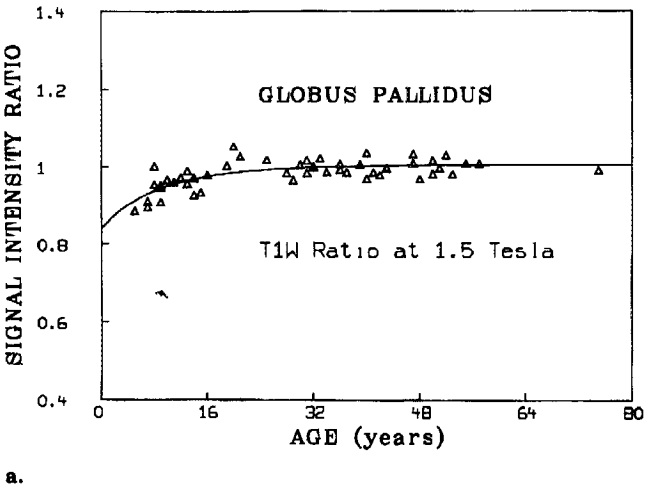
Comparison with Other NMR Studies

It is also important to compare our results from gray/white ratios with other MRI measurements of T1 and T2. Although few reports state a quantitative relationship to iron, we can deduce one by using the Hallgren data to provide estimates of iron contribution (1). By this means, we derive 1/T1 coefficients from several studies at 1.5 Tesla of 3.1 sec^{-1}/mg/g (20) and 2.4 sec^{-1}/mg/g (6), compared with our value of 2.8. This is a good agreement. As for 1/T2, Bartzokis et al. (11) reported data for six adults at 1.5 Tesla that correspond to a coefficient of 38.6 sec^{-1}/mg/g, and Schenk's data on one subject (6) corresponds to 36.2 sec^{-1}/mg/g, versus our value of 40.1 sec^{-1}/mg/g. Other measurements of 1/T2 at 1.5 Tesla, made with an interecho time of only 20 msec, yield 1/T2 coefficients of 30.4 (10), 24.4 (20), and 33.4 sec^{-1}/mg/g (12). These lower values are obviously related to the shorter echo time (see discussion above). Bartzokis et al. (11) also measured T2 at 0.5 Tesla in six adults and reported a field-dependent change in 1/T2 that corresponds to 21.4 sec^{-1}/Tesla/mg/g, compared with our result of 20.3.

Finally, let us compare our findings with in vitro studies of T2 in fresh brain tissue specimens (26). Here it is more convenient to use the zero-field and field-dependent contributions, as we did with ferritin. Our zero-field contribution to 1/T2, 9.6 sec^{-1}/mg/g, agrees well with the in vitro value of 9.0 for a monkey globus pallidus (26, Fig 2), whereas our field-dependent component, 20.3 sec^{-1}/Tesla/mg/g, is in good agreement with a value of 20 obtained in a second globus pallidus (26, Fig 4). It is clear that, despite our use of ratios (see below), our relationships for T1 and T2 are in good agreement with more direct measurements.

Error Discussion

The biggest limitation of our method is the use of SIRs, rather than T1 and T2 values. This was forced by the retrospective nature of the study; there were simply not enough sequences or knowledge of amplifier gains



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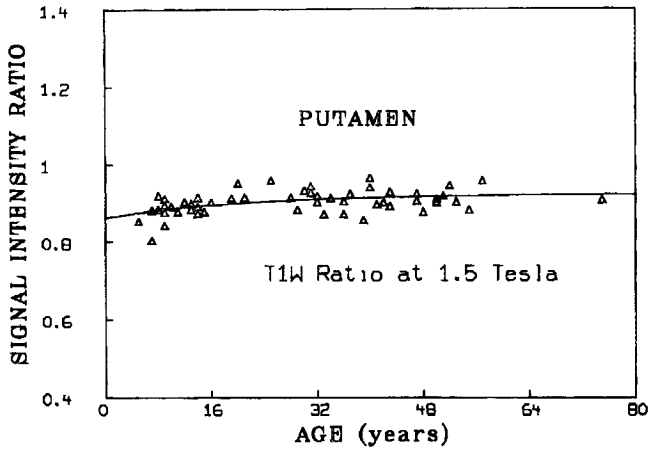

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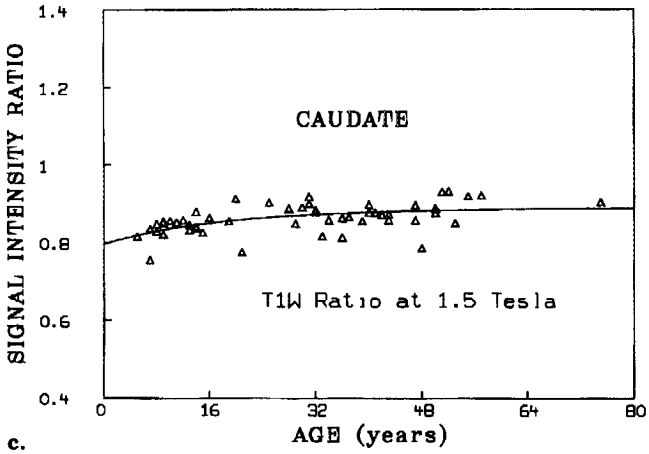


c.

Figure 5. Plots of T1W SIR at 1.5 Tesla versus age of subject. The solid line is a plot of Equations (2 and 3), with parameter *C* determined by curve-fitting. (**a**) Globus pallidus. (**b**) Putamen. (**c**) Caudate nucleus.

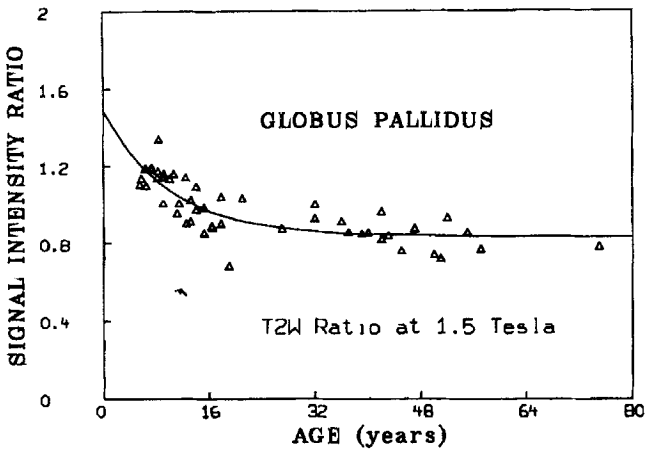
to calculate T1 and T2. The use of ratios prevented us from determining the baseline (zero-iron) values of T1 and T2, and increased the uncertainty in *C* (the coefficient relating 1/T1 to [Fe], because of its dependence on the assumed baseline value *B*. The use of gray/white ratios has also been criticized because the MRI characteristics of white matter may be age-dependent (13), although several authors (9,20) found no significant change in T2 of white matter after age two, and another study found very little variability of T1 or T2 (24). Even if there were such an effect, it would not affect the parameters determined from the interregional data, but would add to the variability. A third problem is the possibility of interregional differences in proton density, as suggested by Drayer (2), who reported lower intensity in the globus pallidus on "density-weighted" scans (TR/TE = 6000/20 msec at 1.5 Tesla). Although this finding could be due (at least in part) to T2-shortening, changes in proton density would indeed alter the parameters of Table 1, although they would not affect the intraregional fits. On the other hand, it must be recognized that calculated values of T1 and T2 from MRI studies are subject to errors, as well (27,28).

All in all, the internal consistency of our data, the relatively small increased variability compared with iron, and the agreement with other NMR studies suggest that the above error contributions are not large. Still they cannot be ruled out, and the potential systematic error from these causes, although not calculable, adds to the purely statistical error estimates given in the tables.

• CONCLUSIONS

We found that the hypothesis that both 1/T1 and 1/T2 of normal gray matter increase linearly with [Fe], from a baseline value, is consistent with both interregional and intraregional MRI data for the frontal cortex, caudate nucleus, putamen, and globus pallidus. From the interregional data, we obtain a contribution of iron to 1/T1 of 2.5 to 2.8 $sec^{-1}/mg/g$, essentially the same at 0.5 and 1.5 Tesla, and a contribution to 1/T2 which is best expressed as a zero-field component of 9.6 $sec^{-1}/mg/g$ and a field-dependent component (from diffusion) of 20.3 $sec^{-1}/Tesla/mg/g$. The second component clearly becomes more important at higher fields. The intraregional age-related changes were mostly in good agreement with these values, although in the putamen the age effect appeared to be diminished. We think it is most significant that the deviations in MRI signal ratio at 1.5 Tesla were consistent with what one would expect from the known variability of iron concentration (except for the cortex with its large partial volume errors). The variability at 0.5 Tesla was larger because of the lower signal/noise ratio.

When compared with relaxation in ferritin solution, the MRI effects were much greater, ranging from a factor of 3 for 1/T1 to a factor of 24 for the zero-field contribution to 1/T2. The difference is attributed to "tissue relaxation enhancement" factors, such as slower diffusion and larger clusters of ferritin, but lack of knowledge of these factors prevents us from making a truly quantitative evaluation. However, the MRI results were



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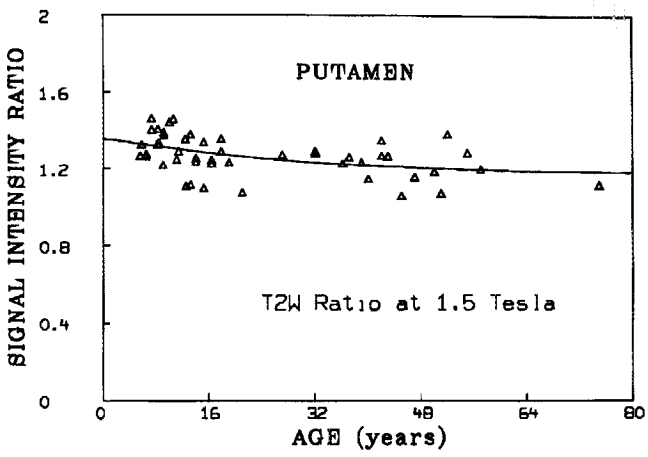

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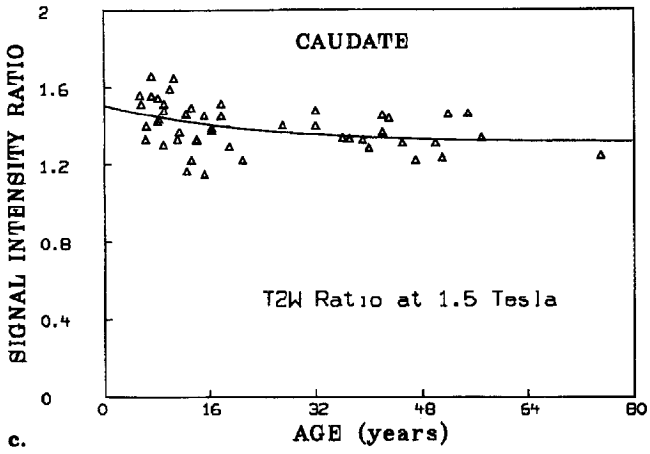

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Figure 6. Same as Figure 5, except T2W ratios, with parameter *E* determined by curve-fitting.

Table 2
Parameters determined by curve-fitting the intraregional SIR vs. age curves (Figs. 5–6) at 1.5 Tesla

	C (sec^{-1}/mg/g)	E (sec^{-1}/mg/g)
Globus pallidus	1.8 (0.2)	42.3 (6.8)
Putamen	1.2 (0.2)	22.9 (3.8)
Caudate	2.6 (0.3)	29.3 (6.3)

Note.—Error estimates (in parentheses) are furnished by the fitting program, and are probably underestimates (see text).

Table 3
Standard deviations of [Fe] (1) and of SIR divided by the average SIR vs. [Fe] slope (Figs. 1–4) for subjects over 30

		SD of SIR Divided by Slope			
	SD of [Fe]	T1W (1.5 T)	T2W (1.5 T)	T1W (0.5 T)	T2W (0.5 T)
Cortex	0.004	0.055	0.034	0.079	0.059
Caudate	0.021	0.036	0.025	0.053	0.046
Putamen	0.034	0.027	0.027	0.043	0.052
Pallidum	0.035	0.019	0.024	0.079	0.059

Note.—Units are mg of Fe/g of tissue.

in excellent agreement with in vitro studies of brain tissue specimens and with other published MRI studies.

In short, the iron hypothesis passed all the tests asked of it. If the observed MRI changes were caused by some other substance, that substance would have to mimic both age-related and interregional changes in iron concentration, it would have to have the same effect on both T1 and T2 as iron, it would have to have the same variability as iron, and it would have to produce the same T2 field dependence. We conclude that it is highly likely that the T1-shortening and T2-shortening, in the gray matter areas studied, are caused primarily by iron in the form of ferritin, resulting in hyperintensity on T1W images and hypointensity on T2W images. Despite all this, we emphasize that the accuracy of our reported coefficients is limited by the use of ratios. We also emphasize that the effect on T2 depends on echo time, and this must be taken into account when comparing or predicting T2 values. Finally, our results do not apply to pathological tissue or, for that matter, necessarily to other normal areas such as the substantia nigra and red nucleus. We intend to do further prospective MRI studies, as well as in vitro studies of brain specimens and of ferritin solutions to better understand and elucidate the quantitative relationships.

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